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(54) Title: DIETARY SUPPLEMENT WITH ANTIOXIDANT ACTIVITY CONTAINING AN ALKANOYL CARNITINE AND A COMBINATION OF POLYPHENOLS EXTRACTED FROM COCOA

(57) Abstract: A health food/dietary supplement with antioxidant activity is described, containing as its characterising components an alkanoyl carnitine and a combination of polyphenols extracted from cocoa.

Dietary supplement with antioxidant activity containing an alkanoyl carnitine and a combination of polyphenols extracted from cocoa

The present invention relates to a health food/dietary supplement comprising as its characterising components an alkanoyl L-carnitine selected from the group comprising isovaleryl L-carnitine and propionyl L-carnitine or their pharmacologically acceptable salts or mixtures thereof and a combination of polyphenols extracted from cacao seeds (*Theobroma cacao*), cocoa powder or chocolate.

It has been found that the aforesaid composition is extremely effective in exerting potent antioxidant, vasculo-protective and anti-inflammatory activity on account of the unexpected synergistic effect exerted by its components. Particularly because of its protective effect against free radicals, the composition according to the invention can be used, in both human subjects and animals, for the prevention and treatment of many vascular and peripheral dysfunctions and diseases of an inflammatory and metabolic type, immune deficiencies, learning disorders and disorders related to ageing, as well as in periods of intense muscular activity which make an increased energy supply advisable.

Isovaleryl L-carnitine, a natural component of the carnitine "pool", presents specific activity at the lysosomal level and on cytosolic calcium movements. It is therefore capable of intervening in proteolytic processes and of protecting a number of organs, such as the liver, against the action of toxic substances.

Propionyl L-carnitine exerts an intense antioxidant effect and is particularly effective in improving the peripheral circulation and cardiac function.

It is known that numerous polyphenols can be extracted from cacao seeds (*Theobroma cacao*) and from chocolate and its derivatives. Fats, phospholipids, amino acids, proteins, fibres and vitamins are also present in these substances.

The polyphenols that characterise cocoa extracts are mainly procyanidines, polyphenols which not only other alimentary products such as wine and tea are rich in, but also the extracts of plants such as *Pinaceae* bark extracts.

Since the procyanidines are bipolymers formed by the union of catechin and epicatechin and since these two monomers are capable of combining through two different types of chemical bonds, numerous isomers can thus be formed even to the extent of producing polymers of substantial molecular weight.

In the case of extracts from cacao seeds (*Theobroma cacao*), most of these are formed, not only by the monomers of catechin and epicatechin, but also by pentamers, hexamers, heptamers and decamers. The biological activity of these extracts, e.g. their immunomodulating activity, appears to be related to the polymers with higher molecular weights, in which, unlike other plant extracts, cocoa extracts are particularly rich.

Their presence, as in the case of oleuropein in olive oil, also serves to prevent the oxidation of the fats present in chocolate. Their antioxidant capacity has been well documented. In the blood of healthy volunteers, it has been possible to observe that the administration of chocolate significantly inhibits the oxidation of LDL, as occurs also in the case of grape, wine or tea catechin extracts.

The theobromine contained in chocolate is 10 times less than that present in tea and 100 times less than that present in coffee, with the result that the consumption of chocolate has been recommended for preventing the incidence of cardiovascular damage, as, for the same reason, has the consumption of red wine and green tea.

Unlike other polyphenols, the epicatechin contained in chocolate is well absorbed in human subjects and the highest plasma peaks are obtained 2-3 hours after ingestion.

On the basis of the results of tests conducted using the compositions according to the present invention, a surprising and unexpected synergistic action of carnitines and polyphenol extracts from cocoa has been detected. Using carnitine complexes in combination with polyphenol extracts from cocoa or with chocolate, an unpredictable enhancement of the effects is achieved with the result that the combination offers prospects of advantageous use in the field of the prevention or treatment of lesions caused by free radicals, cardiocirculatory disorders, atherosclerotic damage and abnormalities caused by ageing, as well as in meeting the increased metabolic energy requirements involved in physical or sporting activities.

Here below are described a number of tests suitable for confirming the surprising synergistic effect of the carnitines and cocoa polyphenol extract or chocolate. A methanolic extract of cocoa powder or defatted chocolate was used in these tests. Both the cocoa powder and the chocolate were dissolved in a 95% methanol and hexane solution. The extract was vacuum evaporated with the addition of water and then centrifuged so as to obtain an aqueous solution in which the polyphenols present were measured according to the Folin-Ciocalteu and Bate-Smith reaction (Bate-Smith, E. C., Chemistry and Industry, 377, 1953), this latter publication being incorporated in this description for reference purposes. Among the various samples of commercially available cocoa powder or choocolate, the one with the highest cocoa concentration (99%) and with a polyphenol concentration of 5.700 mg/l was used.

Anti-lipid-peroxidation activity

In these tests we evaluated the anti-lipid-peroxidation activity of isovaleryl L-carnitine alone, propionyl L-carnitine alone, a carnitine combination, and polyphenol extract from cocoa, as well as of compositions in which the various components were used in combination, by measuring the peroxidation induced in the membranes of red blood cells by hydroperoxides and taking the formation of

malonaldehyde (MDA) as a marker of peroxidation.

For this purpose red blood cells were used from venous blood of volunteers, which, after centrifuging and washing three times in phosphate-buffered saline solution (PBS, 0.015 M, pH 7.4), were diluted in 10 mL of a solution containing 10^{-3} M of PBS-azide. The haemoglobin concentration was measured with Drabkin reagent. The cell suspension contained in 5 mL of PBS-azide with a final haemoglobin concentration of 3.75 mg/mL was exposed to hydrogen peroxide (5 and 20 mM of hydrogen peroxide per ampoule containing 5 mL of cell suspension) which was then incubated at 37°C for one hour.

At the end of the incubation period, lipid peroxidation was calculated using the Stocks and Dormandy method (Stocks, J., Dormandy, T. L., Brit. J. Hematology, 20:95, 1971) which measures the formation of malonaldehyde (MDA) which, in combination with thiobarbituric acid (TBA), forms a coloured chromogen with absorbance at 532 nm (Bird, R. P., Methods Enzymol., 105:299, 1984). The aforementioned publications are incorporated herein by reference.

In this test, samples of test substances were added to ampoules containing the red blood cell suspensions at doses of 100 μg/mL of isovaleryl L-carnitine or propionyl L-carnitine, or 100 μg/mL of a mixture of propionyl L-carnitine, acetyl L-carnitine, L-carnitine and isovaleryl L-carnitine in equimolar amounts, and 100 μg/mL of polyphenol extract from cocoa, respectively. On the basis of the results presented in Table 1, after a 1-hour incubation, the formation of MDA is reduced by propionyl L-carnitine alone, by isovaleryl L-carnitine alone, by the carnitine combination and by the polyphenol extract from cocoa. However, the maximum inhibition of peroxidation induced by hydrogen peroxide is obtained with the combination of propionyl L-carnitine, isovaleryl L-carnitine or the carnitine combination and polyphenol extract from cocoa.

A significant synergistic action of alkanoyl L-carnitines and polyphenol extracts from cocoa is thus detected.

Table 1

Anti-lipid-peroxidation activity test

Treatment	MDA production (nmol MDA/g Hb)
Controls	757.7±66.4
Isovaleryl L-carnitine	610.4±55.5
Propionyl L-carnitine	575.2±53.8
Carnitine combination	518.8±55.2
Polyphenol extract from cocoa	479.6±40.6
Isovaleryl L-carnitine + polyphenol extract from cocoa	205.5±33.3
Propionyl L-carnitine + polyphenol extract from cocoa	192.5±39.4
Carnitine combination + polyphenol extract from cocoa	160.9±30.5

Anti-inflammatory activity

Since both the polyphenols and the carnitines have a favourable action on inflammatory-type tissue reactions, the effects both of isovaleryl L-carnitine alone, propionyl L-carnitine alone, carnitine combination, and polyphenol extracts from powdered and defatted chocolate on the carrageenin-induced inflammatory oedematous reaction in the rat were observed, as were those of compositions in which the various components were combined. The subplanatar zone of the the rat's paw was injected with 0.1 mL of a 1% carrageenin solution (Sigma, St. Louis, U.S.A.). The volume of the carrageenin-induced oedema in the paw was measured using a mercury plethysmograph, one hour after injection of carrageenin and over the subsequent 4-hour period. One hour prior to carrageenin injection, various groups of animals received oral administrations of isovaleryl L-carnitine (300 mg/kg) alone, or propionyl L-carnitine (300 mg/kg) alone, or the same amount of carnitine combination (propionyl L-carnitine, acetyl L-carnitine, L-carnitine and isovaleryl L-carnitine present in equal amounts), or 5

mL/kg of a solution of polyphenol extracts from cocoa or 5 g/kg of defatted chocolate (99% cocoa) or the same products variously combined at the same doses.

Table 2 gives the results of these tests as recorded 2 and 5 hours after carrageenin injection.

As can be seen from the data presented in the Table, all the various products tested are effective in at least partially inhibiting the inflammatory oedematous reaction induced by carrageenin. Surprisingly, however, the most potent inhibitory effect is that obtained with the combination of alkanoyl L-carnitines and chocolate or polyphenol extracts from cocoa. In these conditions, in fact, un unexpected synergistic effect of alkanoyl L-carnitine and chocolate or polyphenol extract from cocoa is detectable.

Table 2

Anti-inflammatory activity test

Treatment	% reduction of carrageenin-induced oedema after	
	2 h	4 h
Isovaleryl L-carnitine	12±9.1	9±0.7
Propionyl L-carnitine	15±0.9	10±0.6
Carnitine combination	16±0.8	12±0.5
Polyphenol extract from cocoa	26±7	25±5
Chocolate (99% cocoa)	18±9.1	20±2.1
Isovaleryl L-carnitine + polyphenol extract from cocoa	39±7.4	48±3.1
Propionyl L-carnitine + polyphenol extract from cocoa	48±5.1	66±5.8
Isovaleryl L-carnitine + chocolate (99% cocoa)	33±3.9	50±4.4
Propionyl L-carnitine + chocolate (99% cocoa)	36±4.4	55±3.9
Carnitine combination + polyphenol extract from cocoa	51.1±7.1	68.2±6.7
Carnitine combination + chocolate (99% cocoa)	49.8±4.4	59.8±6.4

Learning test

The "water maze" method as described by Morris and Lin (Morris, R. J., Neurosci. Meth., 11:47, 1984; Lin, Y, Acta Pharmacol. Sin., 17:1413, 1998) was used for these tests. Mice of both sexes were placed in a maze located in a tank containing water (80 cm × 50 cm × 20 cm) to a depth of 10 cm and, after a suitable period of training, the time taken by the mice to find their way to the end platform was measured. Various groups of animals received oral administrations for 3 days consecutively of isovaleryl L-carnitine (300 mg/kg) alone, propionyl L-carnitine (300 mg/kg) alone, or a complex (200 mg/kg) of different carnitines (propionyl L-carnitine, acetyl L-carnitine, L-carnitine and isovaleryl L-carnitine in equal amounts), or polyphenol extract from cocoa (5 mL/kg) or defatted chocolate (5 g/kg), or compositions containing combinations of the various substances described above at the same doses.

One hour after the last administration, the latency time taken by each animal to reach the platform was estimated. Half an hour prior to the start of the test, all animals received intraperitoneal administrations of scopolamine at the dose of 3 mg/kg. As is known, scopolamine induces abnormalities of spatial orientation and time delays in reaching the platform.

In these tests, too, the results obtained (presented in Table 3 here below) indicate a surprising and unexpected synergistic effect of the carnitines and polyphenol extract from cocoa or chocolate.

Table 3

Learning test

Treatment	Latency time (seconds)
Isovaleryl L-carnitine	29±16
Propionyl L-carnitine	32±14
Carnitine complex	30±10
Polyphenol extract from cocoa	26±8
Chocolate (99% cocoa)	30±9
Isovaleryl L-carnitine + polyphenol extract from cocoa	18±6
Propionyl L-carnitine + polyphenol extract from cocoa	16±4
Carnitine combination + polyphenol extract from cocoa	14±3
Propionyl L-carnitine + chocolate (99% cocoa)	20±8
Carnitine combination + chocolate (99% cocoa)	17±7

Provided here below by way of illustration are a number of non-limiting examples of compositions according to the present invention.

1)	Isovaleryl L-carnitine	500 mg
	Polyphenol extract from cocoa	250 mg
2)	Propionyl L-carnitine	500 mg
	Polyphenol extract from cocoa	250 mg
3)	Isovaleryl L-carnitine	500 mg
	Polyphenol extract from cocoa	100 mg
4)	Propionyl L-carnitine	250 mg
	Polyphenol extract from cocoa	100 mg
5)	Isovaleryl L-carnitine	500 mg
	Cocoa powder (90% cocoa)	1 g

6)	Propionyl L-carnitine	500 mg
	Cocoa powder (90% cocoa)	1 g
7)	Isovaleryl L-carnitine	500 mg
	Chocolate	5 g
8)	Propionyl L-carnitine	500 mg
	Chocolate	5 g
9)	Propionyl L-carnitine	500 mg
	Polyphenol extract from cocoa	250 mg
	Cocoa powder (90% cocoa)	250 mg
10)	Propionyl L-carnitine	250 mg
	Chocolate	5 g
11)	Propionyl L-carnitine	500 mg
	Polyphenol extract from cocoa	250 mg
	Chocolate	5 g
12)	Isovaleryl L-carnitine	100 mg
	Acetyl L-carnitine	100 mg
	L-carnitine	100 mg
	Propionyl L-carnitine	100 mg
	Polyphenol extract from cocoa	300 mg
13)	Isovaleryl L-carnitine	100 mg
	Acetyl L-carnitine	100 mg
	L-carnitine	100 mg
	Propionyl L-carnitine	100 mg
	Polyphenol extract from cocoa	5 g
14)	Isovaleryl L-carnitine	100 mg
	Acetyl L-carnitine	100 mg
	Propionyl L-carnitine	100 mg
	Polyphenol extract from cocoa	300 mg
	Cocoa powder	300 mg

15)	Isovaleryl L-carnitine	100 mg
	Acetiy L-carnitine	100 mg
	L-carnitine	100 mg
	Propionyl L-carnitine	100 mg
	Chocolate	5 g
16)	Isovaleryl L-carnitine	100 mg
	Acetyl L-carnitine	100 mg
	L-carnitine	100 mg
	Propionyl L-carnitine	100 mg
	Polyphenol extract from cocoa	250 mg
	Cocarboxilase	2 mg
	Vit. B_6	5 mg
	Vit. C	50 mg
	Vit. E	5 mg
	Vit. PP	20 mg
	Coenzyme Q_{10}	20 mg
	Selenomethionine	50 µg
17)	Propionyl L-carnitine	100 mg
	Chocolate (99% cocoa)	2 g
	Fructose	100 mg
	Maltose	100 mg
	Destrose	100 mg
	Coenzyme Q_{10}	20 mg
18)	Propionyl L-carnitine	250 mg
	Polyphenol extract from cocoa	250 mg
	Glicine	100 mg
	Lysine	100 mg
	Coenzyme Q_{10}	20 mg

What is meant by a pharmacologically acceptable salt of isovaleryl L-carnitine, L-carnitine or any other alkanoyl L-carnitine is any salt of these with an acid which does not give rise to unwanted toxic or side

effects. These acids are well known to pharmacologists and to experts in pharmaceutical technology.

Non-limiting examples of such salts are the following: chloride; bromide; iodide; aspartate, acid aspartate; citrate, acid citrate; tartrate; phosphate, acid phosphate; fumarate, acid fumarate; glycerophosphate; glucose phosphate; lactate; maleate, acid maleate; mucate; orotate; oxalate, acid oxalate; sulphate, acid sulphate; trichloroacetate; trifluoroacetate and methane sulphonate.

Among these salts, isovaleryl L-carnitine acid fumarate (US 5,227,518) is particularly preferred.

A list of FDA-approved pharmacologically acceptable acids is given in Int. J. Pharm., 33, 1986, 201-217, the latter publication being incorporated in the present specification by reference.

The supplement of the invention may further comprise vitamins, coenzymes, mineral substances, amminoacids and antioxidants. The supplement may be manufactured in the form of tablets, lozenges, capsules, pills, granulates, syrups, vials or drops.

The composition of the invention may also comprise both L-carnitine and further alkanoyl L-carnitines (such as acetyl, butyryl and valeryl L-carnitine). It has been found that supplementation of the characterizing composition (i.e. isovaleryl L-carnitine or propionyl L-carnitine + poliphenol extract from cocoa seeds) with the aforesaid alkanoyl L-carnitines further enhances the synergistic effect of the composition.

Claims

1. A food/dietary supplement which comprises the following characterizing ingredients:

(a) an alkanoyl L-carnitine selected from the group comprising isovaleryl L-carnitine, propionyl L-carnitine or the pharmacologically acceptable salts thereof or mixtures thereof; and

(b) a poliphenol extract from cocoa (*Theobroma cacao*) seeds, cocoa powder or chocolate.

2. The supplement of claim 1, further comprising:

(c) a "carnitine" selected from the group comprising L-carnitine, acetyl L-carnitine, butyryl L-carnitine or the pharmacologically acceptable salts or mixtures thereof.

3. The supplement of anyone of the preceding claims which further comprises vitamins, sugars, coenzymes, mineral substances, aminoacids, peptides and antioxidants.

4. The supplement of any of the preceding claims wherein the pharmacologically acceptable salt is selected from the group comprising: chloride; bromide; iodide; aspartate, acid aspartate; citrate, acid citrate; tartrate; phosphate, acid phosphate; fumarate, acid fumarate; glycerophosphate; glucose phosphate; lactate; maleate, acid maleate; mucate; orotate; oxalate; acid oxalate; sulphate, acid sulphate; trichloroacetate; trifluoroacetate and methane sulphonate.

5. The supplement of any of the preceding claims, for the prevention of lesions caused by free radicals, vascular, cardiac, central or peripheral nervous system alterations, immune deficiencies, learning and ageing-related disorders as well as for meeting increased muscular energy requirements.

6. The dietary supplement of claim 5 in solid, semi-solid or liquid form.

7. The health food/dietary supplement of any of the preceding claims in the form of tablets, capsules, lozenges, pills, granulates, creams, syrups or drops.

8. The supplement of any of the preceding claims, wherein the weight ratio of ingredients (a):(b):(c) ranges from 1:5:2 to 1:0.2:1.

9. The supplement of claim 8, in unit dosage form, comprising:

Isovaleryl L-carnitine	500 mg
Polyphenol extract from cocoa	250 mg

10. The supplement of claim 8, in unit dosage form, comprising:

Propionyl L-carnitine	500 mg
Polyphenol extract from cocoa	250 mg

11. The supplement of claim 8, in unit dosage form, comprising:

Isovaleryl L-carnitine	100 mg
Acetyl L-carnitine	100 mg
L-carnitine	100 mg
Propionyl L-carnitine	100 mg
Polyphenol extract from cocoa	300 mg

12. The supplement of claim 8, in unit dosage form, comprising:

Isovaleryl L-carnitine	100 mg
Acetyl L-carnitine	100 mg
L-carnitine	100 mg
Propionyl L-carnitine	100 mg
Polyphenol extract from cocoa	250 mg
Cocarboxilase	2 mg
Vit. B_6	5 mg
Vit. C	50 mg

Vit. E	5 mg
Vit. PP	20 mg
Coenzyme Q_{10}	20 mg
Selenomethionine	50 µg

13. The supplement of claim 8, in unit dosage form, comprising:

Propionyl L-carnitine	100 mg
Chocolate (99% cocoa)	2 g
Fructose	100 mg
Maltose	100 mg
Destrose	100 mg
Coenzyme Q_{10}	20 mg

14. The supplement of claim 8, in unit dosage form, comprising:

Propionyl L-carnitine	250 mg
Polyphenol extract from cocoa	250 mg
Glicine	100 mg
Lysine	100 mg
Coenzyme Q_{10}	20 mg

15. A method for the prevention and/or treatment of lesions caused by free radicals, vascular, cardiac, central or peripheral nervous systems alterations, immune deficiencies, learning and ageing-related disorders as well as for meeting increased muscular energy requirements, which comprises administering to an individual in need thereof a combination composition comprising the following ingredients:

(a) an alkanoyl L-carnitine selected from the group comprising isovaleryl L-carnitine, propionyl L-carnitine or the pharmacologically acceptable salts thereof or mixtures thereof; and

(b) a poliphenol extract from cocoa (*Theobroma cacao*) seeds, cocoa powder or chocolate.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A23L1/305 A23L1/30 A61K31/205 A61K35/78 A23G1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A23L A61K A23G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, FSTA, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 66914 A (SIGMA TAU HEALTHSCIENCE SPA ;CAVAZZA CLAUDIO (IT)) 29 December 1999 (1999-12-29)	1-8,15
A	claims 1-15 page 1, paragraphs 3,4 page 2, paragraph 4 page 3, line 4-6 page 13, paragraphs 3,5	9-14
X	EP 0 773 020 A (SIGMA TAU IND FARMACEUTI) 14 May 1997 (1997-05-14)	1-8,15
A	claims 1,2,4,7-10; examples 1-13 column 1, line 3-11,33-37,42,43,52-56 column 2, line 8-20 column 4, line 6-16	9-14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Tallgren, A

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 00183 A (SIGMA TAU HEALTHSCIENCE SPA ;CAVAZZA CLAUDIO (IT)) 6 January 2000 (2000-01-06)	1-8,15
A	claims 1-15; examples 1-14; tables 1-3 page 1, paragraphs 1-5 page 2, paragraph 5 -page 3, paragraph 3 page 4, paragraph 8 -page 5, paragraph 3 page 6, paragraph 3 -page 7, paragraph 1	9-14
X	WO 00 28986 A (SIGMA TAU HEALTHSCIENCE SPA ;CAVAZZA CLAUDIO (IT)) 25 May 2000 (2000-05-25)	1-8,15
A	claims 1-15; tables 1-5 page 1, paragraphs 1-5 page 4, paragraph 3 -page 5, paragraph 6	9-14
P,X	WO 01 26666 A (SIGMA TAU HEALTHSCIENCE SPA ;CAVAZZA CLAUDIO (IT)) 19 April 2001 (2001-04-19)	1-8
A	claims 1-4,7-17; examples 1-9; tables 1-4 page 1, paragraphs 3-5 page 2, paragraphs 6,7 page 3, paragraphs 1-3,5,7 page 6, paragraph 5 page 16, paragraph 2	9-14
P,X	WO 01 03683 A (SIGMA TAU HEALTHSCIENCE SPA ;CAVAZZA CLAUDIO (IT)) 18 January 2001 (2001-01-18)	1-8,15
A	claims 1-15; examples 1-10 page 2, paragraph 1 -page 3, paragraph 5	9-14
A	WO 98 33494 A (KOSBAB JOHN V) 6 August 1998 (1998-08-06) claims 1,3,5-13,16-27,30,31; example 1; table 3 page 1, line 9-12 page 3, line 31-33 page 4, line 10-13,23 -page 7, line 14 page 18, line 28-30 page 20, line 9-15 page 21, line 24-30 page 22, line 11-29 page 25, line 6 page 27, line 6 page 34, line 11-19	1-15

INTERNATIONAL SEARCH REPORT

[redacted]ation on patent family members

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